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Patentanmeldung Nr. Patent application No. Demande de brevet n°

98113974.4

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Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Page 2 de l'attestation

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Antisense oligonucleotides inhibiting expression or function of more than one growth factor

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Antisense oligonucleotides inhibiting expression or function of more than one growth factor

A number of antisense oligonucleotides have been described in the prior Art which inhibit expression of either transforming growth factor beta-1 (TGF-ß1) or transforming growth factor beta-2 (TGF-ß2) or transforming growth factor beta-3 (TGF-ß3)

J. EXP. MED. 174 (4), 1991, 925 - 930, Hatzfeld J. et al, "Release of early human hematopoietic progenitors from quiescence by antisense transforming growth factor ß-1 or Rb oligonucleotides" discloses release of early human hematopoietic progenitors from quiescence by antisense transforming growth factor beta-1 or Rb oligonucleotides, where antisense TGF-ß1 negatively regulates the cycling status of early hematopoietic progenitors through interaction with the Rb gene product.

J. NEUROSURG. 78 (1993) 944-51, Jachimczak et al. (1993) and WO 94/25588, Schlingensiepen et al. (1994) teach the use of antisense oligonucleotides targeted to either TGF-ß1 or TGF-ß2 or TGF-ß3.

Proceedings of the National Academy of Sciences of USA, Vol. 88, February 1991, Washington US, pages 1516 - 1520, Potts, J. et al., "Epithelial-mesenchymal transformation of embryonic cardiac antisense oligodeoxynucleotide to transforming growth factor beta 3'" discloses that epithelial-mesenchymal transformation of embryonic cardiac endothelial cells is inhibited by a modified antisense oligodeoxynucleotide to transforming growth factor beta-3 (TGF-ß3). The transformation depends on the activity of a transforming growth factor ß (TGF-ß) molecule produced by the heart. Modified antisense oligodeoxynucleotides generated to non-conserved regions of TGF-ß1, 2, -3 and -4 were prepared in order to examine the possible roles of these members in this transformation. As a result it has been shown that a specific member of the TGF-ß family (TGF-ß3) is essential for the epithelial-mesenchymal transformation.

PROC. NATL. ACAD. SCI 93, (1996), 2909-2914, Fakhrai et al., teaches that transfection of rat 9L gliosarcoma cells with genes encoding antisense sequences to transforming growth factor-beta 2 (TGF-ß2)

sequence comparison between the mRNAs of TGF-beta2, TGF-beta1 and TGF-beta3 showed that not a single sequence of 20 bases in length could be found that would be identical within the three different mRNAs. Even if such a hypothetical sequence had really existed, inhibition of the three mRNAs by such a hypothetical consensus sequence would have been extremely unlikely, since it is well known in the art that only a small minority of antisense sequences complementary to a certain mRNA actually exert a so-called antisense effect, *i.e.* inhibit expression of the respective protein.

Example 1

In the following non-limiting example growth factor secreting tumor cells were incubated with 5 µM of one of the following phosphorothioate modified oligonucleotides in MEM Dulbecco's Medium, supplemented with 10% fetal calf serum:

b1-N17	TCC TCT TCG ACT GCT CTC
b2-N14	CGA AGG TTA AAC CAC TTT CG
b2-N24	GTG AGT CGT GTC GTC C

TGF-ß2-1	C ACA CAG TAG TGC A
TGF-ß2-2	GC ACA CAG TAG TGC
TGF-ß2-3	GC TTG CTC AGG ATC TGC
TGF-ß2-4	TAC TCT TCG TCG CT
TGF-ß2-5	C TTG GCG TAG TAC T
TGF-ß2-6	G TAA ACC TCC TTG G
TGF-ß2-7	GT CTA TTT TGT AAA CCT CC
TGF-ß2-8	GC ATG TCT ATT TTG TAA ACC
TGF-ß2-9	CGG CAT GTC TAT TTT GTA
TGF-ß2-10	G GCA TCA AGG TAC C
TGF-ß2-11	CTG TAG AAA GTG GG
TGF-ß2-12	AC AAT TCT GAA GTA GGG T
TGF-ß2-13	T CAC CAA ATT GGA AGC AT
TGF-ß2-14	GCT TTC ACC AAA TTG GAA GC
TGF-ß2-15	CTG GCT TTT GGG TT
TGF-ß2-16	T CTG ATA TAG CTC AAT CC
TGF-ß2-17	T CCT AGT GGA CTT TAT AG
TGF-ß2-18	T TTT TCC TAG TGG ACT
TGF-ß2-19	C AAT TAT CCT GCA CAT TTC
TGF-ß2-20	GC AAT TAT CCT GCA CA

TGF-ß1-98-13	CCATTAGCACGCGGG
TGF-ß1-98-14	CGGGCTCCG
TGF-ß1-98-15	CCGGCCACCCGGTCGCGG
TGF-ß1-98-16	CGAGCACGGCCTCG
TGF-ß1-98-17	CGGGCAGCGGGCCGGGCG
TGF-ß1-98-18	CGCGGATGGCCTCG
TGF-ß1-98-19	CGATGCGCTTCCG
TGF-ß1-98-20	CCCGCGGCCGGCGGG
TGF-ß1-98-21	CGCAGCCCGGAGGGCG
TGF-ß1-98-22	CGGCGCCCCCCG
TGF-ß1-98-23	CGGCACTGCCGAGAGCGCG
TGF-ß1-98-24	CGGGGATGAAGGCGGCG
TGF-ß1-98-25	CGGGTCGGCGACTCCCG
TGF-ß1-98-26	CGCCTGAGGGACGCCG
TGF-ß1-98-27	AAGCGTCCCCGGCG
TGF-ß1-98-28	CGCGGGGCAGCGTCGCG
TGF-ß1-98-29	CCCCGCGCCTCCGG
TGF-ß1-98-30	CGGCGGCGGCTCG
TGF-ß1-98-31	CGCTCCGGGCCGAGGCCG
TGF-ß1-98-32	CGGCCCCGCGGGCG
TGF-ß1-98-33	CGGACGGGGCGTCC
TGF-ß1-98-34	CGGCCGGGGCCCTCG
TGF-ß1-1	CGA TAG TCT TGC AG
TGF-ß1-2	GTC GAT AGT CTT GC
TGF-ß1-3	CTT GGA CAG GAT CT
TGF-ß1-4	CCA GGA ATT GTT GC
TGF-ß1-5	CCT CAA TTT CCC CT
TGF-ß1-6	GAT GTC CAC TTG CA
TGF-ß1-7	CTC CAA ATG TAG GG
TGF-ß1-8	ACC TTG CTG TAC TG
TGF-ß1-9	GTA GTA CAC GAT GG
TGF-ß1-10	CAC GTA GTA CAC GA
TGF-ß1-11	CAT GTT GGA CAG CT
TGF-ß1-12	GCA CGA TCA TGT TG
TGF-ß1-13	TGT ACT CTG CTT GAA C
TGF-ß1-14	CTG ATG TGT TGA AGA ACA
TGF-ß1-15	CTC TGA TGT GTT GAA G
TGF-ß1-16	GGA AGT CAA TGT ACA G
TGF-ß1-17	CAT GTC GAT AGT CTT GCA
TGF-ß1-18	AGC TGA AGC AAT AGT TGG
TGF-ß1-19	GTC ATA GAT TTC GTT GTG

TGF-ß-1-rwk-8	GA GAG CGC GAA CAG G
TGF-ß-1-rwk-9	CGA GAG CGC GAA CAG
TGF-ß-1-rwk-10	CCC CTG GCT CGG GGG
TGF-ß-1-rwk-11	C CCT GGC TCG GGG
TGF-ß-1-rwk-12	C CCC TGG CTC GGG G
TGF-ß-1-rwk-13	TCC CCC TGG CTC GG
TGF-ß-1-rwk-14	C TCC CCC TGG CTC G
TGF-ß-1-rwk-15	TGC GCT TCC GCT TCA C
TGF-ß-1-rwk-16	CC TCG ATG CGC TTC
TGF-ß-1-rwk-17	G ATG GCC TCG ATG C
TGF-ß-1-rwk-18	G GAT GGC CTC GAT GC
TGF-ß-1-rwk-19	ATG GCC TCG ATG CGC TT
TGF-ß-3-rwk-1	TC AGC AGG GCC AGG
TGF-ß-3-rwk-2	GCA AAG TTC AGC AGG GC
TGF-ß-3-rwk-3	GG CAA AGT TCA GCA GG
TGF-ß-3-rwk-4	GT GGC AAA GTT CAG CAG G
TGF-ß-3-rwk-5	GTG GCA AAG TTC AG
TGF-ß-3-rwk-6	GAC CGT GGC AAA GTT CAG
TGF-ß-3-rwk-7	AGA GAG GCT GAC CGT
TGF-ß-3-rwk-8	GAC AGA GAG AGG CTG AC
TGF-ß-3-rwk-9	A CAG AGA GAG GCT GA
TGF-ß-3-rwk-10	GT GGA CAG AGA GAG G
TGF-ß-3-rwk-11	CA AGT GGA CAG AGA GAG G
TGF-ß-3-rwk-12	TCT TCT TGA TGT GGC C
TGF-ß-3-rwk-13	CC CTC TTC TTC TTG ATG
TGF-ß-3-rwk-14	C ACC CTC TTC TTC T
TGF-ß-3-rwk-15	A TGG ATT TCT TTG GCA T
TGF-ß-3-rwk-16	GGA TTT CTT TGG C
TGF-ß-3-rwk-17	AA GTT GGA CTC TCT TCT C
TGF-ß-3-rwk-18	TAA GTT GGA CTC TCT TCT
TGF-ß-3-rwk-19	GAC CTA AGT TGG ACT C
TGF-ß-3-rwk-20	T TTC TAG ACC TAA GTT GG
TGF-ß-3-rwk-21	CT GAT TTC TAG ACC TAA G
TGF-ß-3-rwk-22	G AAG CAG TAA TTG GTG T
TGF-ß-3-rwk-23	GG AAT CAT CAT GAG G
TGF-ß-3-rwk-24	GGG AAT CAT CAT GAG
TGF-ß-3-rwk-25	G GTT GTC GAG CCG GT
TGF-ß-3-rwk-26	GTC CTC CCA ACA TAG TA
TGF-ß-3-rwk-27	GG GTC CTC CCA ACA

Secretion of TGF-ß2 was inhibited by 18% - 75% in tumor cel

TGF-ß2-14/1 CTT TCA CCA AAT TGG AAG
TGF-ß2-14/2 CAC CAA ATT GGA AGC
TGF-ß2-14/3 TCA CCA AAT TGG AAG C
TGF-ß2-15/1 CTC TGG CTT TTG GG
TGF-ß2-9/1 CGG CAT GTC TAT TTT G

TGF-ß-17-c-2260 ACC TCC TTG GCG TAG TA
TGF-ß-12-9/20-2261 AGG GCG GCA TGT CTA TTT TG
TGF-ß-123-2262 CAG AAG TTG GCA TTG TAC
TGF-ß-12-9/22-2263 AGG GCG GCA TGT CTA TTT TGT A
TGF-ß-23-2268 TGG GAC ACG CAG CAA GG

TGF-ß2-6 G TAA ACC TCC TTG G
TGF-ß2-7 GT CTA TTT TGT AAA CCT CC
TGF-ß2-8 GC ATG TCT ATT TTG TAA ACC
TGF-ß2-9 CGG CAT GTC TAT TTT GTA
TGF-ß2-14 GCT TTC ACC AAA TTG GAA GC
TGF-ß2-15 CTG GCT TTT GGG TT

Secretion of TGF-ß2 was inhibited by 23% - 68% in tumor cells treated with all of the above oligonucleotides compared to untreated control cells.
Secretion of TGF-ß3 was inhibited by 12% - 58% in tumor cells treated with the above oligonucleotides compared to untreated control cells.
In summary these oligonucleotides were capable of inhibiting both TGF-ß2 and TGF-ß3 expression as well as TGF-ß1 expression as demonstrated above.

It is an object of the present invention to provide a method for inhibiting expression and/or function of more than one growth factor with a single molecule. Another object of the present invention is to provide an effective agent which inhibits the growth of tumor cells.
Another object of the present invention is to provide an effective agent which inhibits angiogenesis.
Another object of the present invention is to provide an effective agent which inhibits immunosuppression.
Another object of the present invention is to provide an effective agent which inhibits cell proliferation by inhibiting more than one growth factor.

The present invention also describes a method, wherein the inhibition the synthesis expression and/or synthesis and/or function of multiple growth factors and/or their receptors is achieved with a single oligonucleotide or a combination of oligonucleotides

The present invention also describes a method, wherein the growth factors and/or their receptors are growth factors and/or their receptors involved in angiogenesis.

The present invention also describes a method, wherein the growth factors and/or their receptors are members of the family of transforming growth factor beta growth factors and/or their receptors.

In a preferred embodiment of the invention an oligonucleotide or a combination of two oligonucleotides or a combination of three oligonucleotides is used, capable of inhibiting expression and or function of TGF-ß2 as well as TGF-ß1 and/or TGF-ß3.

In a preferred embodiment of the invention an oligonucleotide or a combination of two oligonucleotides or a combination of three oligonucleotides is used, capable of inhibiting expression and or function of TGF-ß1 as well as TGF-ß3 and/or TGF-ß2.

In a preferred embodiment of the invention an oligonucleotide or a combination of two oligonucleotides or a combination of three oligonucleotides is used, capable of inhibiting expression and or function of TGF-ß3 as well as TGF-ß1 and/or TGF-ß2.

In a preferred embodiment of the invention an oligonucleotide or a combination of two oligonucleotides or a combination of three oligonucleotides is used, capable of inhibiting expression and or function of two or three of the following growth factors and/or their receptors: TGF-ß3 and/or TGF-ß1 and/or TGF-ß2 and/or TGF-ß-Receptor Type I and/or TGF-ß-Receptor Type II and/or VEGF and/or VEGF-Receptor type flt and/or VEGF-Receptor type FLK1/kdr and/or bFGF and/or FGF-Receptors and/or monocyte chemoattractant protein 1 (MCP-1) and/or receptors for monocyte chemoattractant proteins.

In a more preferred embodiment of the invention a sing

genes coding for the following genes TGF-ß3 and/or TGF-ß1 and/or TGF-ß2 and/or TGF-ß3 and/or TGF-ß-Receptor Type I and/or TGF-ß-Receptor Type II and/or VEGF and/or VEGF-Receptor type flt and/or VEGF-Receptor type FLK1/kdr and/or bFGF and/or FGF-Receptors and/or monocyte chemoattractant protein 1 (MCP-1) and/or receptors for monocyte chemoattractant proteins.

In a further preferred embodiment of the invention the nucleic acids coding for sequences complementary to genes coding for the following genes TGF-ß3 and/or TGF-ß1 and/or TGF-ß2 and/or TGF-ß3 and/or TGF-ß-Receptor Type I and/or TGF-ß-Receptor Type II and/or VEGF and/or VEGF-Receptor type flt and/or VEGF-Receptor type FLK1/kdr and/or bFGF and/or FGF-Receptors and/or monocyte chemoattractant protein 1 (MCP-1) and/or receptors for monocyte chemoattractant proteins are used for vaccination.

The present invention also describes a method for combining
- inhibition of different molecules involved in immunosuppression and/or angiogenesis, such molecules including, but not limited to growth factors including, but not limited to Transforming growth factor beta (TGF-ß) including the molecules TGF-ß1, TGF-ß2, TGF-ß3, and/or Cytokines including, but not limited to Interleukin 10 (IL-10) and/or Prostaglandins, including prostaglandin E_2 (PGE_2) and/or TGF-ß-Receptor Type I and/or TGF-ß-Receptor Type II and/or VEGF and/or VEGF-Receptor type flt and/or VEGF-Receptor type FLK1/kdr and/or bFGF and/or FGF-Receptors and/or monocyte chemoattractant protein 1 (MCP-1) and/or receptors for monocyte chemoattractant proteins.

TGF-ß2-27	G CCA CTT TTC CAA G	and/or
TGF-ß2-14/1	CTT TCA CCA AAT TGG AAG	and/or
TGF-ß2-14/2	CAC CAA ATT GGA AGC	and/or
TGF-ß2-14/3	TCA CCA AAT TGG AAG C	and/or
TGF-ß2-15/1	CTC TGG CTT TTG GG	and/or
TGF-ß2-9/1	CGG CAT GTC TAT TTT G	and/or
TGF-ß2-98-1	CATCGTTGTCGTCG	and/or
TGF-ß2-98-2	CGCTTCTTCCGCCG	and/or
TGF-ß2-98-3	CGAAGGAGAGCCATTCG	and/or
TGF-ß2-98-4	CGATGTAGCG	and/or
TGF-ß2-98-5	CGTCAAATCG	and/or
TGF-ß2-98-6	CGTAGTACTCTTCGTCG	and/or
TGF-ß2-98-7	CGCGCTCGCAGGCG	and/or
TGF-ß2-98-8	CGGCCGCCCTCCGGCTCG	and/or
TGF-ß2-98-9	CGCGGATCGCCTCG	and/or
TGF-ß2-98-10	GAGCGCGACCGTGAC	and/or

TGF-ß-17-c-2260	ACC TCC TTG GCG TAG TA	and/or
TGF-ß-12-9/20-2261	AGG GCG GCA TGT CTA TTT TG	and/or
TGF-ß-123-2262	CAG AAG TTG GCA TTG TAC	and/or
TGF-ß-12-9/22-2263	AGG GCG GCA TGT CTA TTT TGT A	and/or
TGF-ß-23-2268	TGG GAC ACG CAG CAA GG	and/or

TGF-ß1-98-1	CGGGGGCGGGGCGGGG	and/or
TGF-ß1-98-2	CGGGGCGGGGCGGGGCG	and/or
TGF-ß1-98-3	CGGCGCCGCCGAGGCGCCCG	and/or
TGF-ß1-98-4	CCGAGGTCCTTGCGG	and/or
TGF-ß1-98-5	CGGCGGTGCCGGGA	and/or
TGF-ß1-98-6	CTCGGCGGCCGGTAG	and/or
TGF-ß1-98-7	CGCTAAGGCG	and/or
TGF-ß1-98-8	CCGCACAACTCCGG	and/or
TGF-ß1-98-9	GCGAGTCGCTGG	and/or
TGF-ß1-98-10	CGGTTGCTGAGGTATCG	and/or
TGF-ß1-98-11	CCGGGAGAGCAACACGG	and/or
TGF-ß1-98-12	CGCTTCTCG	and/or
TGF-ß1-98-13	CCATTAGCACGCGGG	and/or
TGF-ß1-98-14	CGGGCTCCG	and/or
TGF-ß1-98-15	CCGGCCACCCGGTCGCGG	and/or
TGF-ß1-98-16	CGAGCACGGCCTCG	and/or
TGF-ß1-98-17	CGGGCAGCGGGCCGGGCG	and/or
TGF-ß1-98-18	CGCGGATGGCCTCG	and/or

TGF-ß3-98-4	ACGCAGCAAGGCGA	and/or
TGF-ß3-98-5	CGGGTTGTCGAGCCG	and/or
TGF-ß3-98-6	CGGCAGTGCCCCG	and/or
TGF-ß3-98-7	CGGAATTCTGCTCG	and/or
TGF-ß3-98-8	TTCGTTGTGCTCCG	and/or
TGF-ß3-98-9	ATTCCGACTCGGTG	and/or
TGF-ß3-98-10	ACGTGGGTCATCACCGT	and/or
TGF-ß3-98-11	CGAAGAAGCG	and/or
TGF-ß3-312	CCT AAT GGC TTC CA	and/or
VEGF-98-1	CGGCCGCGGTGTGT	and/or
VEGF-98-2	CGGGAATGCTTCCGCCG	and/or
VEGF-98-3	CGGCTCACCGCCTCGGC	and/or
VEGF-98-4	CACGTCTGCGGATC	and/or
VEGF-98-5	CCCCGCATCGCATCAGGG	and/or
VEGF-98-6	CGCCTTGCAACGCG	and/or
VEGF-98-7	CCGACCGGGGCCGG	and/or
VEGF-766	GCT TGA AGA TGT ACCT CG	and/or
VEGF-r-1062	CGT TGC TCT CCG ACG	and/or
flt-1165	GAC ACG GCC TTT TCG	and/or
flt-rm-2115	CCA GCA GCT GAC CAT GG	and/or
flk1/kdr-m-2315	GAA ATC GAC CCT CGG	and/or
MCP-1-Rec-A/B-571	GCA TGT TGT GGA TG	and/or
MCP-1-1954	GCA GAG ACT TTC ATG C	and/or
MCP-1-1955	ATA ACA GCA GGT GAC TGG	and/or
MCP-1-1956	GAA CCC ACT TCT GC	and/or
VEGF-703	CTG CAA GTA CGT TCG	and/or
flt-1567	TCC CTT ATG ATG CCA GCA AGT G	and/or
TGF-ß-Rec-I-796	CCA GCA ATG ACA GC	and/or
TGF-ß-1-rwk-1	G GGA AAG CTG AGG C	and/or
TGF-ß-1-rwk-2	T CGA GGG AAA GCT GA	and/or
TGF-ß-1-rwk-3	C CTC GAG GGA AAG C	and/or
TGF-ß-1-rwk-4	GG GCT GGT GTG GTG	and/or
TGF-ß-1-rwk-5	GA ACA GGG CTG GTG TG	and/or
TGF-ß-1-rwk-6	G AAC AGG GCT GGT G	and/or
TGF-ß-1-rwk-7	AG AGC GCG AAC AGG	and/or
TGF-ß-1-rwk-8	GA GAG CGC GAA CAG G	and/or
TGF-ß-1-rwk-9	CGA GAG CGC GAA CAG	and/or
TGF-ß-1-rwk-10	CCC CTG GCT CGG GGG	and/or
TGF-ß-1-rwk-11	C CCT GGC TCG GGG	and/or
TGF-ß-1-rwk-12	C CCC TGG CTC GGG G	and/or
TGF-ß-1-rwk-13	TCC CCC TGG CTC GG	and/or

C l a i m s

1. A method for the production of nucleic acid molecules, oligonucleotides and their derivatives capable of inhibiting expression and/or synthesis and/or function of two or more growth factors and/or their receptors by selecting oligonucleotide sequences, synthesizing the oligonucleotides and testing their capability to inhibit expression and/or synthesis and/or function of more than one growth factor and/or growth factor receptor in cells.

2. A method according to claim 1 wherein the growth factors and/or growth factor receptors are, selected from the following: TGF-ß3 and/or TGF-ß1 and/or TGF-ß2 and/or TGF-ß4 and/or TGF-ß5 and/or TGF-ß-Receptor Type I and/or TGF-ß-Receptor Type II and/or VEGF and/or VEGF-Receptor type flt and/or VEGF-Receptor type FLK1/kdr and/or bFGF and/or FGF-Receptors and/or monocyte chemoattractant protein 1 (MCP-1) and/or receptors for monocyte chemoattractant proteins and/or bFGF and/or aFGF and/or FGF-receptors and/or interleukins and/or interleukin receptors.

3. A method for the inhibition of expression and/or synthesis and/or function of multiple growth factors and/or their receptors comprising administering a single oligonucleotide or a combination of oligonucleotides obtainable according to any one of the claims 1 or 2.

4. The method according to any of the claims 1 to 3, wherein the growth factors and/or their receptors are growth factors and/or their receptors involved in angiogenesis.

5. The method according to any of the claims 1 to 4, wherein the growth factors and/or their receptors are members of the family of transforming growth factor beta growth factors and/or their receptors.

6. A single molecule obtainable according to the method according to any one of the claims 1 or 2.

7. A combination of molecules obtainable according to the method according to any one of the claims 1 or 2.

TGF-ß2-98-4 CGATGTAGCG and/or
TGF-ß2-98-5 CGTCAAATCG and/or
TGF-ß2-98-6 CGTAGTACTCTTCGTCG and/or
TGF-ß2-98-7 CGCGCTCGCAGGCG and/or
TGF-ß2-98-8 CGGCCGCCCTCCGGCTCG and/or
TGF-ß2-98-9 CGCGGATCGCCTCG and/or
TGF-ß2-98-10 GAGCGCGACCGTGAC and/or

TGF-ß-17-c-2260 ACC TCC TTG GCG TAG TA and/or
TGF-ß-12-9/20-2261 AGG GCG GCA TGT CTA TTT TG and/or
TGF-ß-123-2262 CAG AAG TTG GCA TTG TAC and/or
TGF-ß-12-9/22-2263 AGG GCG GCA TGT CTA TTT TGT A and/or
TGF-ß-23-2268 TGG GAC ACG CAG CAA GG and/or

TGF-ß1-98-1 CGGGGGCGGGGCGGGG and/or
TGF-ß1-98-2 CGGGGCGGGGCGGGGCG and/or
TGF-ß1-98-3 CGGCGCCGCCGAGGCGCCCG and/or
TGF-ß1-98-4 CCGAGGTCCTTGCGG and/or
TGF-ß1-98-5 CGGCGGTGCCGGGA and/or
TGF-ß1-98-6 CTCGGCGGCCGGTAG and/or
TGF-ß1-98-7 CGCTAAGGCG and/or
TGF-ß1-98-8 CCGCACAACTCCGG and/or
TGF-ß1-98-9 GCGAGTCGCTGG and/or
TGF-ß1-98-10 CGGTTGCTGAGGTATCG and/or
TGF-ß1-98-11 CCGGGAGAGCAACACGG and/or
TGF-ß1-98-12 CGCTTCTCG and/or
TGF-ß1-98-13 CCATTAGCACGCGGG and/or
TGF-ß1-98-14 CGGGCTCCG and/or
TGF-ß1-98-15 CCGGCCACCCGGTCGCGG and/or
TGF-ß1-98-16 CGAGCACGGCCTCG and/or
TGF-ß1-98-17 CGGGCAGCGGGCCGGGCG and/or
TGF-ß1-98-18 CGCGGATGGCCTCG and/or
TGF-ß1-98-19 CGATGCGCTTCCG and/or
TGF-ß1-98-20 CCCGCGGCCGGCGGG and/or
TGF-ß1-98-21 CGCAGCCCGGAGGGCG and/or
TGF-ß1-98-22 CGGCGCCCCCCG and/or
TGF-ß1-98-23 CGGCACTGCCGAGAGCGCG and/or
TGF-ß1-98-24 CGGGGATGAAGGCGGCG and/or
TGF-ß1-98-25 CGGGTCGGCGACTCCCG and/or
TGF-ß1-98-26 CGCCTGAGGGACGCCG and/or
TGF-ß1-98-27 AAGCGTCCCCGGCG and/or

VEGF-98-1	CGGCCGCGGTGTGT	and/or
VEGF-98-2	CGGGAATGCTTCCGCCG	and/or
VEGF-98-3	CGGCTCACCGCCTCGGC	and/or
VEGF-98-4	CACGTCTGCGGATC	and/or
VEGF-98-5	CCCCGCATCGCATCAGGG	and/or
VEGF-98-6	CGCCTTGCAACGCG	and/or
VEGF-98-7	CCGACCGGGGCCGG	and/or
VEGF-766	GCT TGA AGA TGT ACCT CG	and/or
VEGF-r-1062	CGT TGC TCT CCG ACG	and/or
flt-1165	GAC ACG GCC TTT TCG	and/or
flt-rm-2115	CCA GCA GCT GAC CAT GG	and/or
flk1/kdr-m-2315	GAA ATC GAC CCT CGG	and/or
MCP-1-Rec-A/B-571	GCA TGT TGT GGA TG	and/or
MCP-1-1954	GCA GAG ACT TTC ATG C	and/or
MCP-1-1955	ATA ACA GCA GGT GAC TGG	and/or
MCP-1-1956	GAA CCC ACT TCT GC	and/or
VEGF-703	CTG CAA GTA CGT TCG	and/or
flt-1567	TCC CTT ATG ATG CCA GCA AGT G	and/or
TGF-ß-Rec-I-796	CCA GCA ATG ACA GC	and/or
TGF-ß-1-rwk-1	G GGA AAG CTG AGG C	and/or
TGF-ß-1-rwk-2	T CGA GGG AAA GCT GA	and/or
TGF-ß-1-rwk-3	C CTC GAG GGA AAG C	and/or
TGF-ß-1-rwk-4	GG GCT GGT GTG GTG	and/or
TGF-ß-1-rwk-5	GA ACA GGG CTG GTG TG	and/or
TGF-ß-1-rwk-6	G AAC AGG GCT GGT G	and/or
TGF-ß-1-rwk-7	AG AGC GCG AAC AGG	and/or
TGF-ß-1-rwk-8	GA GAG CGC GAA CAG G	and/or
TGF-ß-1-rwk-9	CGA GAG CGC GAA CAG	and/or
TGF-ß-1-rwk-10	CCC CTG GCT CGG GGG	and/or
TGF-ß-1-rwk-11	C CCT GGC TCG GGG	and/or
TGF-ß-1-rwk-12	C CCC TGG CTC GGG G	and/or
TGF-ß-1-rwk-13	TCC CCC TGG CTC GG	and/or
TGF-ß-1-rwk-14	C TCC CCC TGG CTC G	and/or
TGF-ß-1-rwk-15	TGC GCT TCC GCT TCA C	and/or
TGF-ß-1-rwk-16	CC TCG ATG CGC TTC	and/or
TGF-ß-1-rwk-17	G ATG GCC TCG ATG C	and/or
TGF-ß-1-rwk-18	G GAT GGC CTC GAT GC	and/or
TGF-ß-1-rwk-19	ATG GCC TCG ATG CGC TT	and/or
TGF-ß-3-rwk-1	TC AGC AGG GCC AGG	and/or
TGF-ß-3-rwk-2	GCA AAG TTC AGC AGG GC	and/or
TGF-ß-3-rwk-3	GG CAA AGT TCA GCA GG	and/or

glomerulonephritis and/or pathological extracellular matrix formation and/or angiogenesis and/or immunosuppression and/or hypoproliferation and/or hyperproliferation of cells.

13.A composition comprising a molecule or combination of molecules according to any of the claims 6 to 10 for the manufacturing of a medicament or a composition to influence cell proliferation, including primary cells in culture such as liver cells chondrocytes, osteoblasts, osteoclasts, keratinocytes, neurons, including neuronal stem cells, cells or the blood lineage, including bone marrow stem cells and other progenitor cells o red and white blood cells.

14.A medicament comprising a molecule and/or a combination of molecules according to any one of the claims 6 to 10 together with additives.

15. The use of molecules according to any of the claims 6 to 10 for inhibiting expression and/or synthesis and/or function of two or more growth factors and/or their receptors by selecting oligonucleotide sequences, synthesizing the oligonucleotides and testing their capability to inhibit expression and/or synthesis and/or function of more than one growth factor and/or growth factor receptor in cells.

16. Oligonucleotides having the sequence

b1-N17 TCC TCT TCG ACT GCT CTC
b2-N14 CGA AGG TTA AAC CAC TTT CG
b2-N24 GTG AGT CGT GTC GTC C

TGF-ß2-98-1 CATCGTTGTCGTCG
TGF-ß2-98-2 CGCTTCTTCCGCCG
TGF-ß2-98-3 CGAAGGAGAGCCATTCG
TGF-ß2-98-4 CGATGTAGCG
TGF-ß2-98-5 CGTCAAATCG
TGF-ß2-98-6 CGTAGTACTCTTCGTCG
TGF-ß2-98-7 CGCGCTCGCAGGCG
TGF-ß2-98-8 CGGCCGCCCTCCGGCTCG
TGF-ß2-98-9 CGCGGATCGCCTCG
TGF-ß2-98-10 GAGCGCGACCGTGAC

TGF-ß3-98-1	TCGAGCTTCCCCGA
TGF-ß3-98-2	CCCGGAGCCGAAGG
TGF-ß3-98-3	CCCGAGGAGCGGG
TGF-ß3-98-4	ACGCAGCAAGGCGA
TGF-ß3-98-5	CGGGTTGTCGAGCCG
TGF-ß3-98-6	CGGCAGTGCCCCG
TGF-ß3-98-7	CGGAATTCTGCTCG
TGF-ß3-98-8	TTCGTTGTGCTCCG
TGF-ß3-98-9	ATTCCGACTCGGTG
TGF-ß3-98-10	ACGTGGGTCATCACCGT
TGF-ß3-98-11	CGAAGAAGCG
TGF-ß3-312	CCT AAT GGC TTC CA
VEGF-98-1	CGGCCGCGGTGTGT
VEGF-98-2	CGGGAATGCTTCCGCCG
VEGF-98-3	CGGCTCACCGCCTCGGC
VEGF-98-4	CACGTCTGCGGATC
VEGF-98-5	CCCCGCATCGCATCAGGG
VEGF-98-6	CGCCTTGCAACGCG
VEGF-98-7	CCGACCGGGGCCGG
VEGF-766	GCT TGA AGA TGT ACCT CG
VEGF-r-1062	CGT TGC TCT CCG ACG
flt-1165	GAC ACG GCC TTT TCG
flt-rm-2115	CCA GCA GCT GAC CAT GG
flk1/kdr-m-2315	GAA ATC GAC CCT CGG
MCP-1-Rec-A/B-571	GCA TGT TGT GGA TG
MCP-1-1954	GCA GAG ACT TTC ATG C
MCP-1-1955	ATA ACA GCA GGT GAC TGG
MCP-1-1956	GAA CCC ACT TCT GC
VEGF-703	CTG CAA GTA CGT TCG
flt-1567	TCC CTT ATG ATG CCA GCA AGT G
TGF-ß-Rec-I-796	CCA GCA ATG ACA GC
TGF-ß-1-rwk-1	G GGA AAG CTG AGG C
TGF-ß-1-rwk-2	T CGA GGG AAA GCT GA
TGF-ß-1-rwk-3	C CTC GAG GGA AAG C
TGF-ß-1-rwk-4	GG GCT GGT GTG GTG
TGF-ß-1-rwk-5	GA ACA GGG CTG GTG TG
TGF-ß-1-rwk-6	G AAC AGG GCT GGT G
TGF-ß-1-rwk-7	AG AGC GCG AAC AGG
TGF-ß-1-rwk-8	GA GAG CGC GAA CAG G
TGF-ß-1-rwk-9	CGA GAG CGC GAA CAG
TGF-ß-1-rwk-10	CCC CTG GCT CGG GGG

A b s t r a c t

A method for inhibiting expression and/or synthesis and/or function of multiple growth factors.